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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/706,659	11/12/2003	Joseph L. Witztum	034123-014	3280

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EXAMINER	
COOK, LISA V	

ART UNIT	PAPER NUMBER
1641	

DATE MAILED: 10/16/2006

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	10/706,659	WITZTUM ET AL.	
	Examiner	Art Unit	
	Lisa V. Cook	1641	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *12 July 2006*.

2a)☒ This action is **FINAL**. 2b)☐ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *27 and 31* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *27 and 31* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date *6/15/06 7/12/06*.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

DETAILED ACTION

Amendment Entry

1. Applicants' response to the Office Action mailed January 12, 2006 (paper filed 7/12/06) is acknowledged. Claims 1-26, 28-30 and 32 have been cancelled. Claims 27 and 31 have been modified. Currently claims 27 and 31 are pending and under consideration.

Non- Compliant Amendment

2. The amendment filed 7/12/06 contained an error with respect to the status identifier for claim 27. Claim 27 is identified as "Previously presented". The claim should be identified as "Currently amended". The Examiner corrected the inadvertent error.

3. Objections and/or rejections of record not reiterated herein have been withdrawn.

Information Disclosure Statement

4. The listing of references in the specification is not a proper information disclosure statement. 37 CFR 1.98(b) requires a list of all patents, publications, or other information submitted for consideration by the Office, and MPEP § 609 A(1) states, "the list may not be incorporated into the specification but must be submitted in a separate paper." Therefore, unless the Examiner on form PTO-892 or Applicant on form PTO-1449 has cited the references they have not been considered. See pages 19 and 20.

5. The Information Disclosure Statements filed 11/12/03 and filed 3/29/04 were considered as to the merits prior to first Acton.

6. The Information Disclosure Statements filed 7/12/06 has been considered as to the merits prior to Final Acton.

REJECTIONS MAINTAINED

Claim Rejections - 35 USC § 101

35 U.S.C. §101 states:

> Whoever invents or discovers any new and useful process, machine, manufacture, or composition of matter, or any new and useful improvement thereof, may obtain a patent therefore, subject to the conditions and requirements of this title.

7. Claims 27 and 31 remain rejected under 35 USC 101 because the claimed invention is directed to non-statutory subject matter.

8. Claims 27 and 31, as written, do not sufficiently distinguish over serum as it exists naturally because the claims do not particularly point out any non-naturally occurring differences between the claimed products and the naturally occurring products. Human antibodies are products of nature.

In the absence of the hand of man, the naturally occurring products are considered non-statutory subject matter. *See Diamond v. Chakrabarty*, 447 U.S. 303, 206 USPQ 193 (1980). The claims should be amended to indicate the hand of the inventor, e.g., by insertion of "Isolated" or "Purified" as taught by page 4 lines 3-20 of specification, for example. See MPEP 2105.

Response to Arguments

Applicant has not included the term "isolated" or "purified" to the claim language to overcome this rejection. Accordingly it is maintained.

Claim Rejections - 35 USC § 112

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

9. Claim 27 remains rejected under 35 U.S.C. 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to enable one skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention. The specification is not enabled for the claimed antibodies because the instant specification is not in compliance with the biological deposit rules. Claims 27-32 are directed to antibodies having particular binding specificity (like IK17, comprising SEQ ID NO:1/SEQ ID NO:2, binding atherosclerotic plaques, binding OxLDL and binding MDA-LDL). However, the claimed antibodies have not been deposited under the provisions of the Budapest treaty. Furthermore, filling of an affidavit or declaration by Applicant or assignee or a statement by an attorney of record who has authority and control over the conditions of deposit over his or her signature and registration number stating that the deposit has been accepted by an International Depository Authority under the provisions of the Budapest Treaty, that all restrictions upon public access to the deposit will be irrevocably removed upon the grant of a patent on this Application and that the deposit will be replaced if viable samples cannot be dispensed by the depository is required.

Without such a statement, it would be impossible for the skilled artisan to practice the invention of claim 27 because other clones made from the source material have no predictable reasonable expectation of success of being identical to the instantly claimed antibodies.

In the absence of any guidance other than to the use of the Mab IK17, one would not know or be able to predict what structure or modifications were important and the amount of experimentation required to determine same would be undue. Note that an enabling disclosure for the preparation and use of only a few analogs of a product does not enable all possible analogs where the characteristics of the analogs are unpredictable.

Accordingly, the art indicates that it would require undue experimentation to formulate and use a successful antibodies as recited in the instant invention without the prior demonstration of specific limitations that have not been recited. Amgen Inc. v. Chugai Pharmaceutical Co. Ltd. (18 USPQ 2d 1027 (CAFC 1991)).

10. Claim 27 remains rejected under 35 U.S.C. 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to enable one skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention.

In particular, claim 27 is drawn to any antibody having the binding specificity of the IK17 antibody, (i) the antibody is specific for oxidation specific epitopes present in the core of atherosclerotic plaques; and (ii) the antibody is specific for oxidized low density lipoprotein and malondialdehyde low density lipoprotein.

Further, it is not known how the monoclonal antibody having single binding specificity will bind both oxidized low-density lipoprotein and malondialdehyde low-density lipoprotein simultaneously. The claims and specification fail to provide the identity or structure of this antibody recognition site.

The specification does not provide evidence of a nucleic acid sequence, other than the sequence of SEQ ID NO: 1 and SEQ ID NO: 2 which are known in the art. From these known sequences primers are produced with the claimed inventive properties; however the specification does not state the identity to a deposited antibody, amino acid sequence, nucleic acid sequence, or any structural characteristics of any other antibody, amino acid sequence, or nucleic acid sequence that has the claimed characteristics.

Moreover, there is evidence that other sequences have not yet been identified therefore; applicants' vague description of an isolated nucleic acid sequence (primers from SEQ ID NO: 1 and SEQ ID NO: 2) has not been adequately described. In view of the lack of evidence, it is apparent that Applicants were not in possession of the unlimited number of primers which may be produced from the known sequences of SEQ ID NO: 1 and SEQ ID NO: 2, at the time of filing the instant application.

The skilled artisan cannot envision the detailed structure of the infinite possible antibodies, amino acid sequences, or isolated nucleic acid sequences, thus conception is not achieved until reduction to practice has occurred, regardless of the complexity or simplicity of the method of isolation. An adequate description requires more than a mere statement that it is part of the invention. The nucleic acid structure is required. See *Fiers v. Revel*, 25 USPQ 2d 1601 at 1606 (CAFC 1993) and *Amgen Inc. V. Chugai Pharmaceutical Co. Lts.*, 18 USPQ2d 1016.

The antibody activity characteristics and tail domain requirements distinguish the antibody only by what it does, i.e., protein activity, which are purely functional distinctions. Even where there is an actual reduction to practice, which may demonstrate possession of an embodiment of an invention, it does not necessarily describe what the claimed invention is. The instant specification and claims describe an isolated monoclonal antibody by its protein function, however this description does not describe the claimed antibody itself. See also, *In The Reagents of the University of California v. Eli Lilly* (43 USPQ2d 1398-1412), where the court held that a generic statement which defines a genus of a compound/seq.id/etc. by only their functional activity does not provide an adequate written description of the genus.
The court indicated that while Applicants are not required to disclose every species encompassed by a genus, the description of a genus is achieved by the recitation of a representative number of molecules, usually defined by a sequence, falling within the scope of the claimed genus. At section B(1), the court states that "An adequate written description ...'requires a precise definition, such as by structure, formula, chemical name, or physical properties', not a mere wish or plan for obtaining the claimed chemical invention".

Thus a skilled artisan cannot envision all the contemplated recognition sequence sites by the detailed chemical structure of the claimed antibody, therefore conception cannot be achieved until reduction to practice has occurred. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the invention commensurate in scope with these claims.

Applicant does not provide guidance for the above noted monoclonal antibodies and provides no guidance as to what modifications or structure are important for the predictable function of the monospecific antibody. Very different structures may be found on antibodies with the same specificity. For example, very different V_H chains can combine with the same V_L chain to produce antibody binding sites with nearly the same size, shape, antigen specificity, and affinity.

A similar phenomenon can also occur when different V_H sequences combine with different V_L sequences to produce antibodies with very similar properties.

These observations indicate that divergent variable region sequences, both in and out of complementarily determining regions, can be folded to form similar binding site contours, which result in similar immunochemical characteristics. Conversely, similar structure may be found on antibodies having different specificities.

Response to Arguments

Applicants have argued that the recent court decision of *Noelle v. Lederman*, 355 F.3d 1343 (Fed. Cir. 2004). *In Noelle*, claims which recite a genus of antibodies that bound to a mouse antigen were found to be unpatentable, because the corresponding human antigen had not been adequately characterized. This is the same issue currently at hand.

Specifically, Applicant's claim 27 is not merely directed to antibodies for the known antigen described in the specification, the IK17- (SEQ ID NO: 1 and SEQ ID NO: 2) but reads on a infinite possibility of unknown antigens having the binding specificity of the IK17 antibody. Therefore the claim is drawn to antibodies from unknown antigens. These antigens have not been shown to be well known and characterized, therefore the rejections under 112, 1st are maintained.

Claim Rejections - 35 USC § 102

11. The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

A person shall be entitled to a patent unless –

(e) the invention was described in a patent granted on an application for patent by another filed in the United States before the invention thereof by the applicant for patent, or on an international application by another who has fulfilled the requirements of paragraphs (1), (2), and (4) of section 371(c) of this title before the invention thereof by the applicant for patent.

The changes made to 35 U.S.C. 102(e) by the American Inventors Protection Act of 1999 (AIPA) and the Intellectual Property and High Technology Technical Amendments Act of 2002 do not apply when the reference is a U.S. patent resulting directly or indirectly from an international application filed before November 29, 2000. Therefore, the prior art date of the reference is determined under 35 U.S.C. 102(e) prior to the amendment by the AIPA (pre-AIPA 35 U.S.C. 102(e)).

I. Claim 27 remains rejected under 35 U.S.C. 102(e) as being anticipated by Witztum et al. (US Patent #6,225,070)

Witztum et al. disclose monoclonal antibodies that specifically bind oxidation-specific epitopes on lipoprotein in blood, arterial tissue and vascular tissue, including atherosclerotic plaque formed in arterial tissue and vascular tissue. See abstract.

Several monoclonal antibodies are disclosed (See tables I and II). E06, E013, E014, and E017 were shown to bind MDA-LDL and oxLDL (Cu 2+ oxidized LDL) – meeting the antibody requirement found on page 4, lines 22-24 of the instant disclosure. The labeled antibodies were employed to image in vivo atherosclerotic plaque (column 10, section B). Various detection procedures are given in column 10, lines 37-53. (therein meeting the limitations of claims 8 and 9). The antibodies are delivery dosage to the host ranges and is dependent on the desired effect (column 14, lines 18-31).

Response to Arguments

Applicant contends that the antibodies taught in US Patent #6,225,070 do not anticipate the instant invention because the antibodies exhibit differential binding to LDL associated epitopes, but none are selected to be specific for MDL-LDL and Cu-OxLDL and any cross-reactivity between the antibodies is merely incidental. This argument was carefully considered but not found persuasive because the claims are directed to the utility of antibodies, fragments, or analogues that are specific for MDL-LDL and Cu-OxLDL but do not bind native LDL. US Patent #6,225,070 discloses antibodies that appear recognize (bind) both MDL-LDL and Cu-OxLDL and not native LDL. See for example US Patent #6,225,070; figure 3 and column 3 lines 14-28. Antibodies E05, E011, E014, E017, and MDA2 do not bind native LDL (see line 6 on figure 3) but bind to both MDA-LDL (see lines 2-5 and 7-9 on figure 3) and CuOx-LDL (see lines 10-14 and lines 15-20 on figure 3).

With respect to the degree of binding it is noted that neither the claims nor the specification require specific binding/non-binding measurements (eliminating cross reactivity) to read over the cited prior art.

In response to applicant's argument that the references fail to show certain features of applicant's invention, it is noted that the features upon which applicant relies (i.e., cross-reactive antibody binding) are not recited in the rejected claim(s). Although the claims are interpreted in light of the specification, limitations from the specification are not read into the claims. See *In re Van Geuns*, 988 F.2d 1181, 26 USPQ2d 1057 (Fed. Cir. 1993).

In response to the argument that the antibodies were not selected for use in the method of imaging atherosclerotic plaques because they recognized both MDA-LDL and Cu-OxLDL, it is noted that the '070 patent uses the antibodies to monitor atherosclerotic plaques (see column 1 line 48 through column 2 line 46, for example) and this is what the instant claims recite. See column 10 line 26 through column 11 line 54.

With respect to the inhibition of Cu-OxLDL uptake by macrophages, it is noted that this is deemed inherent to the antibodies that bind Cu-OxLDL. US Patent #6,225,070 teaches that OxLDL becomes incorporated into plaque lesions during atherogenesis.....and becomes oxidatively modified by various cell types including macrophages. See column 4 lines 32-42. The '070 patent further teaches that the antibodies are useful in defining epitopes and screening for agents to inhibit oxidation-specific LDL epitope binding by macrophages. See column 13 lines 21-26.

Allowable Subject Matter

12. Claim 31 is objected to as being dependent upon a rejected base claim, but would be allowable if rewritten in independent form including all of the limitations of the base claim and any intervening claims.

13. As allowable subject matter has been indicated, applicant's reply must either comply with all formal requirements or specifically traverse each requirement not complied with. See 37 CFR 1.111(b) and MPEP § 707.07(a).

14. For reasons aforementioned, no claims are allowed.

15. **THIS ACTION IS MADE FINAL.** Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the mailing date of this final action.

Remarks

16. Prior art made of record and not relied upon is considered pertinent to the applicant's disclosure:

A. Selley et al. (WO 94/23302) teach an immunological ELISA assay-employing antibodies to measure oxidatively modified human low-density lipoproteins in plasma samples.

B. Holvoet et al. (Journal of Clinical Investigation, Vol.95., No.6., 1 June 1995, pages 2611-2619) disclose a method for detecting MDA-modified LDL. A monoclonal antibody (mAb-1H11) which to bind with MDA-modified LDL ($ka=10^9\ M^{-1}$) and to a much lesser extent with OxLDL (page 2613, column 2, paragraph 1) is described in an immunoassay format.

17. Papers related to this application may be submitted to Group 1600 by facsimile transmission. Papers should be faxed to Group 1600 via the PTO Fax Center located in Crystal Mall 1. The faxing of such papers must conform to the notice published in the Official Gazette, 1096 OG 30 (November 15, 1989). The Group 1641 – Central Fax number is (571) 273-8300, which is able to receive transmissions 24 hours/day, 7 days/week. In the event Applicant would like to fax an unofficial communication, the Examiner should be contacted for the appropriate Right Fax number.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Lisa V. Cook whose telephone number is (571) 272-0816. The examiner can normally be reached on Monday - Friday from 7:00 AM - 4:00 PM.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Long Le, can be reached on (571) 272-0823.

Any inquiry of a general nature or relating to the status of this application should be directed to the Group TC 1600 whose telephone number is (571) 272-1600.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR.

Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see httpr//pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).

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